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TITLE PAGE

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Association of prescribed opioid use between mother and child – a record-linkage study

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Association of prescribed opioid use between mother and child – a record-linkage study

Abstract

Repeated use of prescribed opioids may lead to serious side effects, and it is important to examine risk factors for repeated use. The aim of this study was to investigate the association between maternal use of prescribed opioids and the use of prescribed opioids by their offspring.

Data were drawn from two nationwide registers linked by the unique person identity numbers: the Norwegian Population and Housing Census in 2001 and the Norwegian Prescription Database (2004-2009). The study population consisted of 97,574 adolescents aged 15-16 years in 2001 and their mothers. Repeated use of opioids was defined as filling 4+ and 15+ prescriptions during 2004-2009 by the offspring and mothers, respectively. Non-steroidal anti-inflammatory drugs (NSAIDs) are not potentially addictive, and were used as a reference analgesic drug group.

The proportion of repeated users were higher among individuals whose mothers were registered with repeated use of opioids (8.4 %) compared to those with mothers without repeated use (2.4 %). Odds ratio was 3.1 (95% CI 2.7-3.6) when adjusted for mothers socioeconomic characteristics and the gender of the offspring. Low maternal socio-economic status increased the risk of repeated opioid use among their offspring. Maternal repeated use of NSAIDs increased the likelihood of repeated use of NSAIDs among offspring OR 1.8 (95% CI 1.7 – 2.0).

Introduction

Approximately 10 % of the Norwegian population received at least one opioid prescription for analgesia in 2009 [1]. This number has been increasing steadily over the years parallel to that of many other developed countries [2-10]. Increased efforts to address the assumed under-treatment of pain [11] may be one explanation, as extensive literature has shown that pain management is critical in order to achieve a favorable quality of life and improve medical outcome [12].

Opioids have been the mainstay of pain treatment for thousands of years, and remain so today [13]. Its use has been and still is the focus of considerable debate due to its double-edged nature in terms therapeutic effect and serious side effects. Prescription opioids are highly effective when used properly [14] and are generally of low organ toxicity [15], but long-term use may be problematic because of the risk of addiction and misuse [14]. As it is unlikely that other classes of analgesic drugs will supersede the opioids in the very near future [11] it is important to identify those at high risk of developing problematic use of opioids before initiating treatment. One way to achieve this is to identify potential risk factors through epidemiological studies.

Tsuang and colleagues recognize drug abuse as the culmination of a series of transitions of drug involvement from drug exposure to drug abuse. Drug abuse is preceded by a series of acquisition steps that are necessary, but not sufficient for its development [16]. In developed countries therapeutic

prescription of opioids adds to several steps of this chain of transitions; exposure, sporadic use and regular use. In that context, use of prescribed opioids plays an important role in the potential development of opioid abuse. Drugs abuse is thought to be a result of both genetic and environmental risk factors [17] which is supported by evidence that liability to illicit drug use and abuse aggregates in families [18]. To our knowledge, updated information on the influence of maternal use of prescribed opioids on prescribed use in their offspring, as a separate factor and in relation to other socioeconomic characteristics of the household, is limited. Therefore, it would be interesting – and important in a public health perspective – to investigate the reproduction of use of potentially addictive prescription drugs across generations. In Norway all citizens are assigned a unique 11-digit identification number, enabling linkage of available register information on drug use and socioeconomic characteristics, on an individual level [19]. It is also possible to link together members within the same household. Thus, based on nationwide register information, the aim of this study were to investigate the association between maternal use of prescribed opioids and the use of prescribed opioids by their offspring.

Methods

Data from The Population and Housing Census in 2001 (Census 2001) and the Norwegian Prescription Database (NorPD) were linked by using the unique 11-digit identification number, assigned to all individuals living in Norway. The record linkage was approved by the Norwegian Data Inspectorate and has been endorsed by the Regional Committee for Medical Research Ethics.

The Population and Housing Census in 2001 – information on socioeconomic data

Information on socioeconomic variables was retrieved from the nationwide population and housing census in Norway 2001 (Statistics Norway), performed November 3rd 2001 [20]. These variables are based on information from several administrative registers and contain information on all citizens living in Norway. Each individual is registered with a family number, enabling linkage of individuals within the same household. In this context, individuals registered within the same household do not necessarily imply a biological family relationship between individuals. However, according to administrative registers 97.6 % of all children aged 0-17 years were living with their biological mother in Norway in 2000, at the time when the nationwide population and housing census was performed (Statistics Norway, 2001). Thus, adult females within the household will be referred to as mothers throughout the paper. The following variables were included in our analysis; mothers educational level, mothers activity status/labour force participation (employed, unemployed, in education, or receipt of national insurance benefit (disability-, retirement- or survivor pension)), marital status and age.

The Norwegian Prescription Database – information on drug use

Prescription data on analgesics during 2004–2009 were drawn from the NorPD, which covers all of Norway's 4.8 million inhabitants. From January 1, 2004, all pharmacies in Norway have been obliged by law to send in electronic data on all redeemed prescriptions to the Norwegian Institute of Public

Health [19]. NorPD contains information on all individuals who have received prescription drugs dispensed at pharmacies. All prescriptions, reimbursed or not, are stored in the database and the drugs are classified according to the anatomical therapeutic chemical (ATC) classification [21]. Data on opioids (ATC code N02A, main outcome variable) and non-steroidal anti-inflammatory drugs (NSAIDs, ATC code M01A, comparator) were used. Codeine, tramadol and dextropropoxyphene make up the weak N02A-opioids on the Norwegian market, while the following strong N02A-opioids are available: morphine, hydromorphone, oxycodone, ketobemidone, phetidine, fentanyl, buprenorphine and tapentadol [22]. All N02A-opioids require prescriptions in Norway. Parallel to opioid drugs, NSAIDs have analgesic properties, but without the potential of being addictive. For this reason NSAIDs was used as reference. The data collected were: patient unique identifying number (encrypted), sex, age, age at death in case of death during the period, reimbursement code, the dispensing date and drug information (ATC code and number of defined daily doses (DDD)).

The outcome variable, repeated use of opioids among offspring, was defined as receiving four or more opioid prescriptions during 2004–2009. By using this limit the repeated users consist of the highest 10 percentile of opioid users. This cut-off was chosen to exclude users who received opioids for minor incidents such as dentistry and accidents. Repeated use among mothers' was defined similarly by the highest 10 percentile, which gave a cut-off of 15 or more prescriptions. The same 10 percentile cut-off was used for the comparator. Reimbursement codes held in the database were used to identify patients receiving analgesics for cancer treatment.

The study population

Our analysis are restricted to data on citizens aged 15-16 years in 2001 and their mothers, participating in the nationwide population and housing census in Norway in 2001 and registered living in the same household that year. Children born in 1985-86 were selected (n= 108,163), of whom 285 were excluded because of situations such as; registered as parents themselves, not living in a private household, or living in cohabitation (Figure 1). The mother was defined as the oldest female person registered with the same family number as the 15-16 year old. This may have led to misclassifying grandmothers as mothers, but only 5 of the classified mothers were > 50 years at the time of the classified offspring's birth. In total 657 were excluded, in whom the oldest female or male registered in the same household was 15 years or younger at time of birth. In families with more than one 15-16 year old, only the firstborn were included. The 107,221 15-16 year olds were distributed in 104,214 families, in which 5,725 were excluded due to being registered living without their mothers and 915 were excluded because the mother and/or their offspring received opioids to treat cancer related pain. The remaining 97,574 mother-child pairs were included in the analysis. The outcome variable, repeated use of opioids among offspring, was obtained during 2004-2009, when the children were 18-24 years of age.

Statistics

Odds ratios (OR) with 95% confidence intervals (CI) for variables potentially associated with opioid use, were estimated by logistic regression. Maternal characteristics such as mothers' use of opioids,

educational level, activity status/labour force participation, marital status and age were included in the model as independent variables together with the offspring's gender. In total, 95,819 of the 97,574 families included in the logistic regression had complete data on all the variables in the analysis (1.8 % missing). All analyses were done using SPSS 15.0 for Windows. Cochran-Armitage test for linear trend was used to examine a possible dose-response relationship between the proportion of offspring opioid users with the number of maternal opioid prescriptions. Level of significance was set to $p < 0.05$.

Results

Table 1 shows the socioeconomic characteristics of the mothers according to opioid use status. Overall a socioeconomic gradient was observed between mothers who were repeated opioid users during 2004-2009 compared to the rest of the study-population. Educational level was significantly lower among maternal users, a larger proportion of the maternal users were receivers of a disability pension, fewer were registered as employed as compared to the non users, and a higher proportion of the maternal users were not married (or a registered partner).

Of the 97,574 offspring eligible for analysis, 2,519 (2.6 %) were classified as repeated users of opioids during 2004-2009. The proportion of repeated users were higher among individuals whose mothers were registered with repeated use of opioids (8.4 %) compared to those with mothers without repeated use (2.4 %) (Table 2). Odds ratio was 3.7 decreasing to 3.1 when adjusting for other variables. Several of the variables based on characteristics of the mothers were independently associated with repeated opioid use among offspring: lower educational level, disability pensioner and not having a registered partner or husband. In addition, female offspring were more likely to use opioids repeatedly compared to males (Table 2).

A possible dose-response relationship was observed, with the proportion of offspring opioid users increasing with more frequent maternal opioid use. This was evident for various degrees of offspring opioid use ($p < 0.001$ for all categories) (Figure 2).

A total of 5,267 offspring (5.4 %) were repeated users of NSAIDs during 2004-2009. Maternal repeated use of NSAIDs increased the likelihood of repeated use of NSAIDs among offspring OR 1.8 (1.7 – 2.0) (Table 3). Mothers' socioeconomic status was also predictive of repeated use of NSAIDs.

Discussion

Our study showed that repeated maternal use of opioids was associated with a threefold increased risk of repeated opioid use among their offspring. The proportion of offspring opioid users increased with increasing maternal opioid use, suggesting a dose-response relationship.

The association observed for repeated maternal and offspring use of NSAIDs may indicate that reproduction of drug use patterns is present for all classes of analgesics drugs. This may be due to inherited pain thresholds and/or habits of how to cope with- and treat pain.

We are not aware of other studies which specifically have examined the association between prescribed maternal and offspring opioid use. However, our results are in agreement with the findings in studies examining the association between parental and offspring illicit opioid use [17]. Evidence does suggest that the liability to illicit drug use and abuse aggregates in families, a phenomenon that may be explained by both genetic and environmental factors [18]. This might as well be the case with potentially addictive prescription drugs, as shown by a recent study conducted by Hartz and colleagues which found an association between maternal and offspring use of benzodiazepines/z-hypnotics, OR 1.9 (1.8 – 2.0) [23]. It is however, very important to emphasize that our cut-off points of 15+ prescriptions of opioids among mothers and 4+ prescriptions among their offspring do not indicate problematic use of opioids or abuse. It is not possible to separate appropriate from problematic use based on our data.

In terms of genetics, inheritable diseases that require or make opioid treatment more probable can explain some of the association observed in our study. In addition, inherited differences in pharmacokinetics and effect of opioids that increases the vulnerability to the development of problematic opioid use may be another contributing factor.

When taking environmental factors into account, being exposed to maternal opioid use may, as proposed by Tsuang, act as the first step on the way to opioid drug use. This is evident for illicit use and may also be true for therapeutic use. Additionally problematic use among offspring may be explained by negative life events associated with problematic maternal use [17].

Maternal characteristics indicating a lower socio-economic position (low education and disability pension) were independently associated to use of opioids among offspring. Considering the potentially harmful effect of these drugs, our results are in line with former research into health inequalities showing that lower socio-economic status is correlated with poorer habits of health behavior [24-25]. Thus, use of potentially addictive drugs may constitute yet another type of poor health behaviour, along with making unhealthy food choices, physical inactivity and smoking which is documented to be more prevalent among socio-economic disadvantaged groups [26].

Medicine use among young people in general is documented to be widespread and increasing [27-30]. Use of drugs for a variety of complaints among young females in particular, grows considerably during the teenage years [31]. One qualitative study exploring the use of analgesics revealed that young women relied on analgesics to cope with perceived pressures and social anxieties, as part of their attempt to meet everyday goals involving performance and participation [32]. Our study adds to the evidence that females are at a higher risk of becoming repeated users compared to men.

Even though many relevant confounders associated with opioid use are included in our model, we don't have any data on pain, the main indication of use, among the offspring. Thus, analgesic drug use increases significantly with more self-reported pain in this age group [33]. As a result, the observed difference may be explained by more cases of pain among offspring with mothers repeatedly using opioids.

We chose a 90-percentile cut-off for repeated use of opioids in order to exclude users who received opioids for minor incidents such as dentistry and accidents. A recent study from the United States showed that dentists were the main prescribers of opioids for patients aged 10-19 (31 %) and the second most frequent among those aged 20-29 (17 %) [10]. Lack of information on indication for opioid treatment makes it hard to determine whether our chosen cut-off point is ideal. In total, 24.5 % of the offspring retrieved at least one prescription on an opioid during the study period, while only 2.7 % received four or more prescriptions. Thus, repeated opioid use constituted about 10 % of the offspring opioid users in this study.

In this study repeated use of opioid included all opioids regardless of subclass. A more detailed analysis of patterns of use, including distinction between stronger/weaker and long-acting /short-acting opioids would have been desirable. Use of codeine in combination with paracetamol and tramadol do account for nearly the entire opioid consumption among younger generations [34]. As a result we could not stratify for strong/weak and long-acting/short-acting opioids due to few strong and long-acting opioid users.

Compliance is always an issue when using prescription based data. We don't have any data on the extent to which purchased drugs were actually taken. However, our data are based on dispensed drugs rather than prescribed which at least rules out primary non-compliance [35]. Finally our reference drug group may not be ideal as NSAIDs can be used either with or without a prescription, and we lack information on non-prescription use.

Other weaknesses include: 1) maternal characteristic valid in 2001 may have changed when data on drug use was collected in 2004-2009, 2) we do not know whether mother's drug use precedes that of the child, or vice versa.

During our six year study period 2.6 % of the offspring were classified as repeated users of opioids. Considering that cancer patients are excluded and that diseases requiring opioid therapy are quite rare in this age group, this number is high. In order to minimize the risk of problematic use of opioids, identifying factors associated to use is important. Our study suggests that repeated maternal use of opioids may be associated with repeated use of opioids among offspring.

No conflicts of interest are known to the authors.

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Figures and tables

Figure 1: Flow chart of the study population. Collected from the Population and Housing Census in 2001

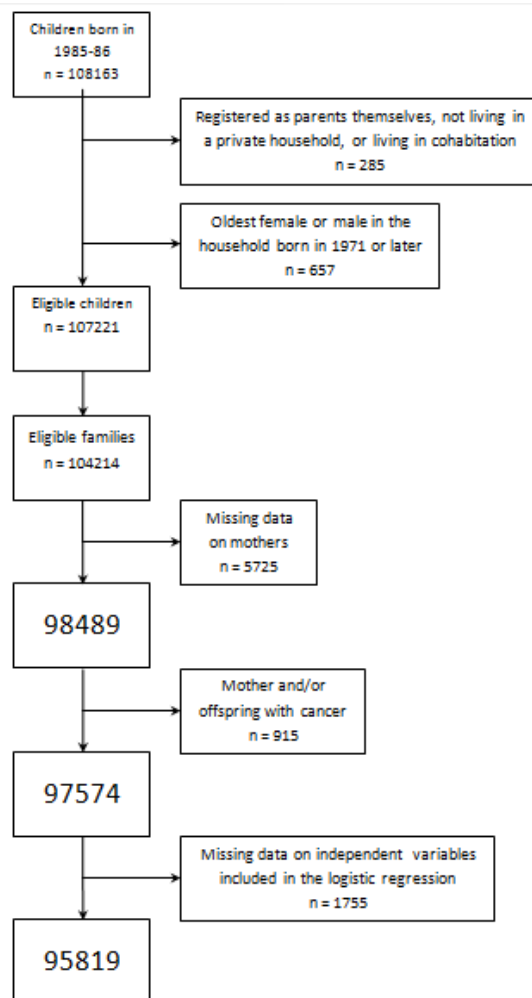


Figure 2: The proportion of opioid users (various degrees) among offspring based on maternal use of opioids

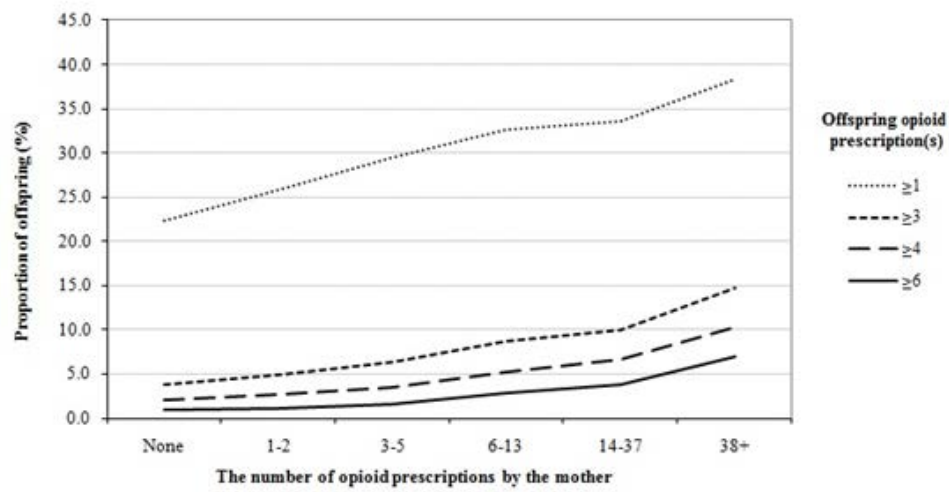


Table 1. Socioeconomic characteristics of mothers with 15-16 year old children in 2001, according to use of opioids in 2004-2009.

	Repeated maternal use of opioids during 2004-09 ¹		p-value
	No (N = 94423)	Yes (N = 4066)	
Mother age (mean(SD))	43.0 (5.0)	42.0 (5.3)	< 0.001
Mother educational level ²			< 0.001
<i>low (junior high school)</i>	11.4 % (10544/92763)	21.8 % (865/3962)	
<i>medium (senior high school)</i>	58.8 % (54561/92763)	63.3 % (2508/3962)	
<i>high (college, university)</i>	29.8 % (27658/92763)	14.9 % (589/3962)	
Mother activity status ³			< 0.001
<i>employed</i>	83.9 % (79206/94413)	59.3 % (2411/4066)	
<i>unemployed</i>	1.3 % (1219/94413)	2.0 % (82/4066)	
<i>student</i>	1.5 % (1402/94413)	2.0 % (80/4066)	
<i>disability pensioner</i>	3.3 % (3099/94413)	19.6 % (796/4066)	
<i>old-age pensioner</i>	0.3 % (282/94413)	0.4 % (16/4066)	
<i>other</i>	9.7 % (9205/94413)	16.7 % (681/4066)	
Mother married/registered partner	74.9 % (70720/94423)	60.0 % (2441/4066)	< 0.001

¹ Repeated use among the mothers equals 15+ prescriptions during 2004-2009 (Upper 10 percentile)

² 1764 missing (1.8 %)

³ 10 missing (0.01 %)

Table 2: Maternal opioid use, and other factors associated with use of opioids among offspring

	Repeated use of opioids among offspring (2004-2009) ¹				
	Prevalence % (n)	Unadjusted OR OR (95 % CI)	p-value	Adjusted OR ² OR (95 % CI)	p-value
Repeated maternal use of opioids³					
No	2.4 % (2172/92220)	1.0	-	1.0	-
Yes	8.4 % (304/3599)	3.7 (3.3 – 4.2)	0.000	3.1 (2.7 – 3.6)	0.000
Gender (offspring)					
Male	1.9 % (940/48940)	1.0	-	1.0	-
Female	3.3 % (1536/46879)	1.7 (1.6 – 1.8)	0.000	1.7 (1.6 – 1.9)	0.000
Mother's educational level					
High (college, university)	1.7 % (476/28011)	1.0	-	1.0	-
Medium (senior high school)	2.8 % (1598/56530)	1.7 (1.5 – 1.9)	0.000	1.4 (1.3 – 1.6)	0.000
Low (junior high school)	3.6 % (402/11278)	2.1 (1.9 – 2.4)	0.000	1.7 (1.4 – 1.9)	0.000
Mother's activity status					
Employed (n = 80929)	2.4 % (1920/80278)	1.0	-	1.0	-
Unemployed (n = 1241)	3.4 % (42/1225)	1.5 (1.1 – 2.0)	0.016	1.1 (0.8 – 1.5)	0.463
Student (n = 1437)	2.8 % (40/1430)	1.2 (0.9 – 1.6)	0.245	1.0 (0.7 – 1.3)	0.864
Old-age pensioner (n = 279)	3.6 % (10/275)	1.6 (0.9 – 2.9)	0.130	1.2 (0.6 – 2.2)	0.611
Disability pensioner (n = 3800)	4.6 % (168/3688)	2.0 (1.7 – 2.4)	0.000	1.4 (1.2 – 1.6)	0.000
Other (n = 9032)	3.3 % (296/8923)	1.4 (1.2 – 1.6)	0.000	1.1 (1.0 – 1.3)	0.033
Mother married / registered partner					
Yes	2.3 % (1608/71169)	1.0	-	1.0	-
No	3.5 % (868/24650)	1.6 (1.5 – 1.7)	0.000	1.4 (1.3 – 1.5)	0.000

¹ Repeated use among the offspring equals 4+ prescriptions during 2004-2009 (Upper 10 percentile)

² Adjusted for gender, maternal use of opioids, mother's educational level, mother's activity status, age and if mother is married or has a registered partner

³ Repeated use among the mothers equals 15+ prescriptions during 2004-2009 (Upper 10 percentile)

Table 3: Maternal use, and other factors associated with use of NSAIDs among offspring

	Repeated use of NSAIDs among offspring (2004-2009) ¹				
	Prevalence % (n)	Unadjusted OR OR (95 % CI)	p-value	Adjusted OR ² OR (95 % CI)	p-value
Repeated mat. use of NSAIDs³					
No	5.1 % (4526/88824)	1.0	-	1.0	-
Yes	9.4 % (661/6995)	1.9 (1.8 – 2.1)	0.000	1.8 (1.7 – 2.0)	0.000
Gender (offspring)					
Male	3.6 % (1776/48940)	1.0	-	1.0	-
Female	7.3 % (3411/46879)	2.1 (1.1 – 1.3)	0.000	2.1 (2.0 – 2.2)	0.000
Mother's educational level					
High (college, university)	3.6 % (1021/28011)	1.0	-	1.0	-
Medium (senior high school)	6.0 % (3399/56530)	1.7 (1.6 – 1.8)	0.000	1.6 (1.4 – 1.7)	0.000
Low (junior high school)	6.8 % (767/11278)	1.9 (1.8 – 2.1)	0.000	1.7 (1.5 – 1.9)	0.000
Mother's activity status					
Employed (n = 80929)	5.2 % (4200/80278)	1.0	-	1.0	-
Unemployed (n = 1241)	5.5 % (67/1225)	1.0 (0.8 – 1.3)	0.721	0.9 (0.7 – 1.1)	0.354
Student (n = 1437)	4.5 % (64/1430)	0.9 (0.7 – 1.1)	0.200	0.8 (0.6 – 1.0)	0.038
Old-age pensioner (n = 279)	6.9 % (19/275)	1.3 (0.8 – 2.1)	0.226	1.2 (0.7 – 1.9)	0.447
Disability pensioner (n = 3800)	8.0 % (296/3688)	1.6 (1.4 – 1.8)	0.000	1.4 (1.2 – 1.5)	0.000
Other (n = 9032)	6.1 % (541/8923)	1.1 (1.0 – 1.3)	0.003	1.0 (0.9 – 1.1)	0.478
Mother married / registered partner					
Yes	5.2 % (3669/71169)	1.0	-	1.0	-
No	6.2 % (1518/24650)	1.2 (1.1 – 1.3)	0.000	1.1 (1.0 – 1.2)	0.001

¹ Repeated use among the offspring equals 4+ prescriptions during 2004-2009 (Upper 10 percentile)² Adjusted for gender, maternal use of NSAIDs, mother's educational level, mother's activity status, age and if mother is married or has a registered partner³ Repeated use among the mothers equals 15+ prescriptions during 2004-2009 (Upper 10 percentile)